Screening Programmes

A Laboratory Guide to Newborn Screening in the UK for

CONGENITAL HYPOTHYROIDISM

First Edition / February 2014

NHS Newborn Blood Spot Screening Programme
www.newbornbloodspot.screening.nhs.uk
A Laboratory Guide to Newborn Screening in the UK for Congenital Hypothyroidism

Handbook for laboratories incorporating:

- Background to the CHT Screening Programme
- General organisation
- Screening protocol
- Pre-analytical factors
- Analysis of thyroid-stimulating hormone (TSH)
- Preterm repeat policy
- Clinical follow-up and referral
- Reporting and communication of results
- Laboratory standards and guidelines
- Quality and performance monitoring
- Data collection and audit
- References

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About the NHS Newborn Blood Spot Screening Programme

The NHS Newborn Blood Spot Screening Programme has responsibility for developing, implementing and maintaining a high quality, uniform screening programme for all newborn babies and their parents. The UK National Screening Committee (UK NSC) recommends that all babies in the UK are offered screening for phenylketonuria, congenital hypothyroidism (CHT), sickle cell disease (SCD), cystic fibrosis (CF) and medium-chain acyl-CoA dehydrogenase deficiency (MCADD). There is a service specification for the NHS Newborn Blood Spot Screening Programme (No.19) available as part of the public health functions exercised by NHS England (www.gov.uk/government/publications/public-health-commissioning-in-the-nhs-from-2013).

The UK NSC and NHS Screening Programmes are operated by Public Health England (PHE). PHE’s mission is to protect and improve the nation’s health and to address inequalities through working with national and local government, the NHS, industry and the voluntary and community sector. PHE is an operationally autonomous executive agency of the Department of Health.

This is the first edition of the guide

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Appendix 1 CHT Initial Clinical Referral Standards and Guidelines (January 2013)

Appendix 2 British Paediatric Surveillance Unit (BPSU) study – UK Surveillance of Primary Congenital Hypothyroidism in Children Aged 5 Years and Under (UK CHT)

Appendix 3 Communication Guidelines: When Congenital Hypothyroidism is Suspected

Appendix 4 Template for notification of presumptive positive for designated paediatrician (by screening laboratory to clinician)
1.1 Background
All babies across the UK are offered a blood test for congenital hypothyroidism (CHT) as part of the national newborn blood spot screening programme.

As stated in the 1981 Standing Medical Advisory Committee guidelines, screening for CHT aims to detect infants who do not produce adequate thyroxine from birth because their thyroid gland has not developed at all or has failed to develop properly, or who cannot produce active thyroid hormone due to an inherited deficiency, known as ‘dyshormonogenesis’ (Department of Health and Social Security, 1981).

Screening for CHT was formally introduced as a national newborn screening programme in England and Wales in June 1981. Screening was already taking place in Scotland (1979) and Northern Ireland (1980).

The programme is a service to babies and their parents and seeks to balance the interests of parents whose children are identified as having CHT and the majority, whose children are unaffected.

The original UK Newborn Screening Programme Centre standards and guidelines for clinical referral (2005) for CHT were reviewed during 2012-2013 by a multidisciplinary Joint Standing Committee on Screening for Congenital Hypothyroidism (www.newbornbloodspot.screening.nhs.uk/cht).

The Joint Standing Committee, through consultation processes with stakeholders, devised national screening and follow-up diagnostic protocols for CHT together with updated standards and guidelines for clinical referral. The UK National Screening Committee (UK NSC), via the Blood Spot Advisory Group has endorsed the protocols, the standards and guidance recommended by the Joint Standing Committee and these are the basis for this first edition of a laboratory handbook (UK Newborn Screening Programme Centre, 2012a; UK Newborn Screening Programme Centre, 2013).

This handbook is provided for newborn screening laboratories as a guide to support service provision in the UK and is available together with other relevant documents on the NHS Newborn Blood Spot Screening Programme website (www.newbornbloodspot.screening.nhs.uk).

At the time of going to print, every attempt has been made to provide the correct, up-to-date information. If there are any errata or comments, please send them to the NHS Newborn Blood Spot Screening Programme at phe.screeninghelpdesk@nhs.net for incorporation into the next edition.

1.2 Scope and purpose
This document provides guidance for those laboratories which provide a newborn blood spot screening service for CHT in the UK. It is intended to define a framework for the pre-analytical, analytical and post-analytical steps in the newborn screening process so that a consistent approach is maintained. Built into this framework is guidance on achieving good quality by application of standards and audit.
1.3 Scientific background to the screening protocol

CHT is a disorder which results in inadequate thyroid hormone production by the thyroid gland. The thyroid gland produces thyroxine (T4), a hormone essential for normal growth and development and is regulated by thyroid-stimulating hormone (TSH – also known as thyrotropin) produced by the pituitary gland. At approximately 20 weeks gestation, the foetus’ thyroid gland should commence producing thyroxine as the mother’s thyroxine supply fails to meet demands. The current TSH-based screening test may not detect all those preterm infants (especially those born between 23 and 27 weeks gestation) whose TSH levels may not be increased at 5-8 days of age, mainly due to the immaturity of the hypothalamic-pituitary axis.

CHT may arise from a number of different aetiologies. Primary CHT involves abnormality of the thyroid gland – its absence (agenesis), or abnormal development (dysgenesis) which could involve being displaced (ectopic thyroid), growth suppressed by maternal ‘anti-thyroid’ medication, or foetal thyroid of normal location and size, but non-functioning or diminished capacity in producing thyroxine (dyshormogenesis). Hypothyroidism may also be caused by inadequate supply of TSH (known as secondary hypothyroidism). The majority of all CHT cases are sporadic. Only a small percentage having a genetic component (Pollitt et al., 1997).

Figure 1. Congenital Hypothyroidism – Aetiology

Thyroid dysgenesis occurs mostly as a sporadic disease, but a genetic cause has been identified in about 2% of cases. Genes associated with thyroid dysgenesis include several thyroid transcription factors expressed in the early phases of organogenesis as well as genes like the thyrotrophin receptor gene expressed later during gland morphogenesis. Data adapted from LaFranchi (2013).

Primary CHT symptoms include coarse facial features, enlarged protruding tongue, cold mottled skin, low hair line, large posterior fontanelle, umbilical hernia, jaundice, constipation, feeding difficulties and lethargic behaviour. Babies may be clinically affected at birth but to an extremely varied degree and few display all listed symptoms and many are asymptomatic at birth (Pollitt et al., 1997).
Secondary hypothyroidism due to pituitary failure will not be detected through the CHT Screening Protocol and will account for up to 5% of all CHT cases (UK Newborn Screening Programme Centre, 2012a).

Transient hypothyroidism occurs when babies are biochemically hypothyroid, then later revert to normal thyroxine levels naturally. The majority of these babies are sick, preterm (<37 weeks gestation) neonates and the process is not well understood. This is very rare in full term babies (37-41 weeks gestation) and congenital hypothyroidism detected via newborn blood spot screening in full term babies is likely to be permanent. Preterm infants are potentially susceptible to transient hypothyroidism due to immaturity of thyroid function, other acute illness and exposure to iodine-containing compounds in imaging and/or surgery. However, Bijarnia et al. (2011) suggested that there is no conclusive evidence that preterm infants are of increased risk of CHT relative to full term infants (UK Newborn Screening Programme Centre, 2012a).

There are also cases reported of babies with low T4 and normal TSH levels in the initial newborn blood spot screening specimen, who later display an abnormally elevated TSH and are subsequently diagnosed with congenital hypothyroidism. Half of these babies with this abnormal profile were preterm. These babies may not be detected by newborn blood spot screening using TSH only (Mandel et al., 2000).

Children with a confirmed diagnosis of CHT should be treated with oral levothyroxine sodium with minimal delay. The objective of treatment is to normalise TSH within the first month. The dose of levothyroxine may need to be reduced if TSH is suppressed or if the baby is showing signs of overtreatment. Babies with significant endogenous thyroid hormone production may need smaller initial doses. Once treatment commences, TSH and thyroid hormone concentration are closely monitored so that levels are maintained within accepted ranges to enable normal growth and intellectual function.

The Initial Clinical Referral Standards and Guidelines (2013) state that babies in whom a diagnosis of CHT has been made should commence treatment by 14 days of age (see Appendix 1 - CHT suspected on initial screening sample – Standard 18a).

Long-term follow-up studies have documented excellent outcomes among children with CHT for whom an appropriate dosage of thyroid hormones is established soon after birth (Grosse & Van Vliet, 2011). Children who have very low levels of thyroxine before treatment (possibly because they had more severe CHT, or because treatment was started later) had an IQ at age ten that was 10 points lower than normal. Children who had slightly higher thyroxine levels before starting treatment had normal IQs (Jones & Donaldson, 2009). Whilst it is known that newborn screening can prevent severe disability in babies with CHT, it is not known whether treatment for babies with CHT can reverse any effects of hypothyroidism caused before the baby was born. If so, it is thought that these effects will only be small (Donaldson & Jones, 2013).

In cases where the cause or persistence/permanence of hypothyroidism has not been confirmed, confirmatory testing should be undertaken by stopping treatment at 2-3 years of age with subsequent monitoring of thyroid function (see Appendix 1 CHT Initial Clinical Referral Standards and Guidelines – Diagnostic Protocol). Where permanent CHT has been established, treatment is expected to be life-long.

Patients with permanent hypothyroidism will require long-term monitoring and follow-up. This is particularly so for female patients due to the risks for the foetus during pregnancy.

The NHS Newborn Blood Spot Screening Programme is currently funding a British Paediatric Surveillance Unit study on CHT (see Appendix 2), one of the aims is to determine the incidence of the condition in the UK. Several papers quote an incidence of about 1 in 3,000 (Mandel et al., 2000; LaFranchi, 2010). The condition is more common in females than in males.
1.4 General organisation

CHT screening is fully integrated within the existing blood spot screening programme and based on the same screening laboratory populations. The initial screening test, the assay of TSH, uses blood collected on the standard newborn screening blood sample collection card. Quality assurance and performance management arrangements follow the same general principles as those for other newborn screening programmes.

With CHT, as for other blood spot screening programmes, the screening laboratory is a major communication hub. Screening results are fed back to child health records departments (CHRDs), with onward transmission of negative results to the parents via health visitors. While over 99% of results are ‘CHT not suspected’ and generated promptly, in the case of premature infants who required repeat testing at 28 days, tests will not be completed until the baby is over a month old. Where the screening result report is used by the CHRD to check for completeness of coverage the effect of the CHT screen on the timeliness of this process needs to be taken into account. There should be a system for acknowledging the receipt of specimens in the laboratory separately from reporting the test results (using status code 01) – see section 9.1.
2.0 The screening protocol

The CHT screening protocol is intended to:

- **Maximise** the early detection of CHT so that pre-symptomatic treatment can be initiated to reduce the long-term morbidity associated with the condition if untreated

- **Minimise**
  - Second heel pricks
  - Diagnostic delay

2.1 The screening protocol

This protocol is summarised diagrammatically in Figure 2. No alternative is recommended.

The initial screening sample – thyroid stimulating hormone (TSH) analysis is performed on a single spot from the initial dried blood sample.

Babies in whom the TSH concentration is <8 mU/L whole blood (WB) (analytical cut-off*) in the initial screening sample should be considered to have a negative screening result for CHT and should be reported as **CHT not suspected**.

Samples with TSH greater than or equal to a preliminary threshold of 8 mU/L WB are retested in duplicate from the same card but on a different spot(s).

Action is taken on the triplicate mean result.

Babies in whom the mean TSH concentration in the initial screening sample is:

- <10 mU/L WB (action cut-off) - should be considered to have a negative screening result for CHT and should be reported as **CHT not suspected**

- ≥20 mU/L WB - should be considered to have a positive screening result for CHT and should be reported as CHT suspected. They are referred to the paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with special interest in CHT or experience in managing these patients. See chapter 8 – Clinical follow-up and referral

- ≥10 mU/L and <20 mU/L WB - should be considered to have a borderline result for CHT and should be reported as **CHT borderline**. A repeat dried blood spot sample should be requested to be taken 7-10 days after the initial sample and assayed for TSH in duplicate (ideally discs punched from different spots)

Babies in whom the mean TSH concentration in the repeat screening sample is:

- <10 mU/L WB - should be considered to have a negative screening result for CHT and should be reported as **CHT not suspected**

- ≥10 mU/L WB - should be considered to have a positive screening result for CHT and should be reported as **CHT suspected**. They are referred to the paediatric endocrine team (regional
specialist team) or to a clearly identified lead paediatrician with special interest in CHT or experience in managing these patients. See chapter 8 – Clinical follow-up and referral.

* The analytical cut-off is set at 20% below the screen action cut-off of 10 mU/L WB to allow for the natural variation in the TSH assay (i.e. the coefficient of variation, CV = 10%) and to minimise the effect of volumetric variability that occurs in dried blood spots.

For a summary of the rationale and definition of cut-offs used in the screening protocol – see section 4.4.

**Figure 2. CHT screening protocol**

2.2 Sibling testing

Diagnostic testing conducted to confirm a case from newborn screening may provide additional information on recurrence. Recurrence is unusual in the case of thyroid dysgenesis but there is likely to be autosomal recessive inheritance with a 1:4 recurrence risk for families of babies with thyroid dyshormogenesis.
No ‘early’ screening for siblings (prior to day 5, counting day of birth as day 0) is recommended. Due to the neonatal TSH surge in the first few hours of life, screening using this protocol cannot be accurately completed until TSH has decreased, usually after a few days.

The blood spot sample should be taken on day 5 and in exceptional circumstances between day 5 and day 8 for all babies regardless of medical condition, milk feeding and prematurity. This is to enable timely detection of abnormal results and initiation of appropriate treatment.

2.3 Unscreened babies

Babies who have not been screened during the newborn period should be screened (dried blood spot TSH) up to 12 months of age in line with NHS Newborn Blood Spot Screening Programme guidance. After 12 months of age, if the family or GP have any clinical concerns a referral for paediatric assessment would be appropriate.

A form (see section 2.3.1) has been developed by the Joint Standing Committee on Screening for CHT Diagnostic Outcomes Sub-group to assist the identification, investigation and reporting of babies/children diagnosed with congenital hypothyroidism and not identified through the newborn screening programme up to 5 years of age. This may involve the paediatric endocrine teams, regional specialist teams, lead paediatricians, newborn screening laboratories and regional quality assurance leads/area teams.

2.3.1 Notification form

This form has been developed to assist communication between the relevant organisations and provides a record of critical points in the investigation. The details also enable the NHS Newborn Blood Spot Screening Programme to evaluate the CHT Screening Programme and share any lessons learned from an investigation.

The form is available from the NHS Newborn Blood Spot Screening Programme website (www.newbornbloodspot.screening.nhs.uk/cht).

The form should be completed as far as possible by the responsible clinician prior to sending to colleagues in the screening laboratory. All forms containing identifiers should be sent and received via secure nhs.net email addresses.

The form should have all fields shaded in grey removed prior to sending to the NHS Newborn Blood Spot Screening Programme. There should be no identifiable data on the form. Once completed, please forward to phe.screeninghelpdesk@nhs.net as an attachment.

2.4 Previously screened babies with subsequent discrepant result

Raised TSH concentration ≥10 mU/L WB on sample taken where there is a previous CHT not suspected result in a baby born ≥32 weeks gestation.

In the event that a repeat sample requested for screening purposes for another condition or unrequested additional repeat has been unavoidably analysed CHT and a discrepant result has emerged from the original screening result, the following should be used as a guide:

- Contamination is unlikely
- Follow the CHT Screening Protocol. The revised screening result for the baby needs to be carefully communicated to the appropriate health professional for onwards transmission to the parents
3.0 Pre-analytical factors

3.1 Family history and other risk factors

Babies presenting with clinical symptoms, discussed in section 1.3, or babies known to be at risk due to family history should be regarded as high risk and should be investigated independently according to clinical circumstances as well as being screened in the normal way.

In cases where additional testing has been undertaken before routine screening it is advantageous for the results to be communicated to the screening laboratory. Where such results are communicated this may avoid unnecessary duplication of follow-up or diagnostic testing.

3.2 Specimen requirements

Blood spot sampling should be according to the ‘Guidelines for Newborn Blood Spot Sampling’ (UK Newborn Screening Programme Centre, 2012b). Further information is available at [www.newbornbloodspot.screening.nhs.uk](http://www.newbornbloodspot.screening.nhs.uk). Specimens should be transported to the laboratory in the usual way and kept in a dry environment at room temperature or 4°C before analysis; storage after analysis should follow the guidelines provided by the in the document ‘Policies and standards for newborn blood spot screening in the UK’ (UK Newborn Screening Programme Centre, 2005).

Venepuncture or venous/arterial sampling from an existing line is an alternative method to collect the blood spot sample. This is providing the sample is not contaminated with EDTA/heparin and the line is cleared of infusate. The use of heparinised capillary tubes is not recommended. Anticoagulants may affect the assay.

Although TSH is relatively stable (see section 4.3), samples received in the laboratory more than 14 days after the date of collection are unsuitable for testing and a repeat sample must be requested as soon as possible. This is a general requirement for all dried blood spot screening tests.

Samples taken when the baby is >12 months old should not analysed (see section 2.3).

3.3 Factors affecting the screening result

The newborn experiences a TSH surge post birth which peaks at 30 minutes of age. Levels decrease slowly until 5-7 days of age (Fisher & Klein, 1981).

Secondary hypothyroidism due to generalised pituitary failure or isolated TSH deficiency will not be detected through the CHT Screening Protocol and will account for up to 5% of all CHT cases (UK Newborn Screening Programme Centre, 2012a).

There are a number of factors which could cause false negative and false positive results; these may be due to process errors, contamination/interference or have a physiological basis (e.g. the presence of maternal antibodies or acute illness). If there is any suspicion about the integrity of the sample, it should be rejected and a repeat requested.

3.3.1 Potential for false negative results

Several factors are known to lower TSH concentrations in babies with CHT, leading to falsely negative screening results.

**Insufficient/inadequate.** If the blood does not fully percolate to the reverse side of the sample paper the measured TSH could be falsely low, leading to a false negative result.
Compressed spots. When the blood sample has been taken, the blood spot must not be compressed. Applying pressure reduces the density of blood on the card and can lead to a false negative result.

Prematurity. Evidence suggests that preterm infants, especially those born between 23 and 27 weeks gestation, are at higher risk of hypothyroxaemia at the time of the first routine screening test due to a number of factors, including immaturity of thyroid function (primarily the hypothalamic-pituitary axis), the effects of acute illness and/or the use of iodine-containing compounds in imaging and surgery. See chapter 7 for the CHT Preterm Repeat Protocol.

Thirty weeks gestation appears to be a critical gestational age in terms of thyroid regulation (Ogilvy-Stuart, 2002). Compared with term infants, postnatal free T4 increases are lower in 31 to 34 week infants, attenuated in 28 to 30 week infants and absent in 23 to 27 week infants. Physiological evidence suggests that 28 days is the postnatal age by which maturation of thyroid function occurs in most very preterm infants (Williams et al., 2004).

Delayed postnatal elevation in TSH concentrations (hypothalamic-pituitary hypothyroidism). There are also cases reported of low T4 and normal TSH levels in the initial newborn blood spot screening specimen in babies who later display an abnormally elevated TSH and are subsequently diagnosed with congenital hypothyroidism. Half of these babies with this abnormal profile were preterm. These babies may not be detected by newborn blood spot screening (Mandel et al., 2000).

Blood transfusion. This could result in a false negative result, as for other screening tests, and a repeat sample should be taken after a reasonable time has elapsed. At least 72 hours is recommended, as for the other screening tests, to allow pre-transfusion levels to be reached.

It is not practicable to adopt alternative diagnostic approaches routinely in these babies. It must always be borne in mind that not all cases of CHT will be detected on newborn screening and that any child showing appropriate symptoms should be investigated accordingly.

3.3.2 Potential for false positive results

A false positive is where the TSH result is confirmed on retest in duplicate on the original blood spot sample or repeat blood sample (also in duplicate) as elevated (screen positive) but is not confirmed on follow-up i.e. confirmatory diagnostic testing results are normal. In practice it may be impossible to differentiate an incorrect/artefactual result on the screening specimen from a genuine increase of TSH which is transient and not present at diagnostic follow-up. Possible causes of a ‘false positive’ include:

Early sampling. Due to the neonatal TSH surge in the first few hours of life, screening using this protocol cannot be accurately completed until TSH has decreased, usually after a few days. Screening for CHT should not be undertaken prior to day 5 (counting day of birth as day 0).

Multi-layering. The CHT screen requires a good quality blood spot for the TSH assay. Specimens that are over-layered by multiple applications are likely to give falsely raised results and could lead to a false positive screening result.

Transient hypothyroidism. Transient hypothyroidism is when babies are biochemically hypothyroid, then later become biochemically euthyroid. Preterm infants are potentially susceptible to transient hypothyroidism due to immaturity of thyroid function, other acute illness, drug induced, maternal-antibody induced or due to excess maternal iodine supplements (transfer from mother to infant via the placenta or breast milk). Exposure to iodine-containing compounds in imaging and/or surgery can also cause the thyroid in the foetus or neonate to temporarily decrease function to protect against hyperthyroidism (Wolff-Chaikoff effect). Transient hypothyroidism may also be idiopathic.
Iodine deficiency: Maintenance of thyroid function depends on the availability of dietary iodine. Hypothyroidism related to maternal iodine deficiency is rare in Western iodine-sufficient populations.
4.0 The TSH assay

Thyroid stimulating hormone (TSH) in the routine newborn screening blood spot is to be assayed using a methodology that has been demonstrated to be fit-for-purpose and approved by the Joint Standing Committee on Screening for CHT. Ideally the reagents and instrumentation should be CE marked. The laboratory should follow the procedures detailed in the manufacturer’s instructions. Procedures for specimen identification and disc punching are similar to those for the immunoreactive trypsinogen (IRT) screening assay.

The sensitivity and specificity of the CHT screen are crucially dependent on the performance of the TSH assay.

4.1 Internal quality and performance monitoring
Internal quality control samples covering at least two and ideally three TSH levels should be included with each analysis batch. Each laboratory should assign acceptable ranges for these samples.

Dried blood spots available from the Centres for Disease Control and Prevention (CDC) can also be used for internal quality control purposes and achieve levels of precision (coefficient of variation) of approximately 7 to 10% at TSH concentrations of approximately 10 and 20 mU/L whole blood. Each laboratory should assess and regularly monitor their own precision profiles.

4.2 External quality assessment
Laboratories should participate in an approved external quality assurance scheme (e.g. UK National External Quality Assessment Scheme (UK NEQAS)), and demonstrate acceptable performance.

4.3 Stability of TSH in blood spots
Thyroid stimulating hormone (TSH) is relatively stable. It has been reported that when stored in refrigerators between 4-8 °C (in sealed plastic bags, packed in closed boxes without added desiccants) the TSH levels declined significantly only when re-assayed at 48 or 60 months. TSH was reported to be stable for a period of 3 years (Lando et al., 2008). Waite et al. (1987) found that there was no significant difference in mean TSH when samples were stored at either -20 °C or 4 °C (both with and without a sealed bag and silica gel) or external ambient temperatures between 4-30 °C for a period of up to 30 days. However, Mei et al. (2011) found that statistically significant differences did exist between storing samples in -20°C with desiccant rather than at ambient temperatures (between 1-40 °C) regardless of length of storage.

It is inadvisable to rely on a screening result from a sample that has been significantly delayed in transit – empirically the reliability of results from samples received 14 days after collection should be regarded as suspect and a repeat specimen requested. However, if a high result is obtained from a sample analysed >14 days after collection it should be processed according to the national protocol.

4.4 Rationale and definition of TSH cut-offs
Analytical cut-off:
The initial screening samples are normally assayed in singleton. Those with TSH results equal to or above a preliminary threshold (8 mU/L whole blood) are then re-assayed in duplicate to give a more
definitive result. This is to minimise effects of volumetric variability of the punched discs, day-to-day variation in TSH assay calibration, and to detect possible sample misidentification. The value used for the analytical cut-off is set at 20% below the screen action cut-off of 10 mU/L whole blood (WB) to allow for this natural variation (CV = 10%) and unless there is significant variation in the calibration of a particular kit lot, should not need to be changed.

**Action cut-off:**

Grosse and Van Vliet (2011) state that a cut-off of 10 mU/L WB should be sufficient to detect permanent CHT due to thyroid dyshormogenesis.

The rate at which blood TSH concentration declines/stabilises/with age varies in babies with transient or atypical hypothyroidism can be very variable. As such, it is expected that the CHT Screening Protocol will detect, or fail to detect, a small number of cases that will later be classified as false negative and false positive due to the variable nature of the condition.

According to a recent systematic evidence review (Knowles and Olafsdottir, 2013), the positive predictive value varies with cut-off level and is optimised with either a single positive cut-off of around 20 mU/L WB or borderline cut-off levels over 10 mU/L WB. Using borderline cut-off levels below 10 mU/L WB, significantly increases the number of repeat specimens required and may affect the risk/benefit balance.

The cut-offs are being reviewed as part of the British Paediatric Surveillance Unit study on Congenital Hypothyroidism – see Appendix 2.
5.0 The first screening specimen

TSH analysis is performed frequently enough to permit referral of screen positive results within 2-4 working days of sample receipt. Samples are initially assayed in singleton.

For babies with TSH values less than the analytical cut-off of 8 mU/L whole blood (WB), a negative result CHT not suspected is issued. For babies born less than 32 weeks gestation a repeat request should be issued (status code 03 “repeat sample required for CHT preterm” – see CHT Preterm Repeat Policy in chapter 7).

Samples with TSH greater than or equal to 8 mU/L WB should be re-assayed in duplicate with the next batch. Where possible the samples for re-assay should be taken from two separate spots on the card. The average of the three results should be taken.

The set of triplicate results should be reviewed for consistency as poor analytical performance can produce different results; a spuriously high result can occur with blood spot layering or may be low if there is a missing spot or poor sample.

5.1 Results from duplicate re-assay

If the average TSH concentration is:

- below 10 mU/L (action cut-off) and provided there is no suspicion of a ‘missing spot’, a negative result: CHT not suspected, is issued - unless the baby was born less than 32 weeks gestation – in this case, a repeat request should be issued (status code 03 “repeat sample required for CHT preterm” - see CHT Preterm Repeat Policy in chapter 7)

If the results are consistent and the average TSH concentration is:

- equal to or above 20 mU/L WB, a positive result: CHT suspected, is issued and the baby referred – regardless of their gestational age at birth (see chapter 8)

- equal to or above 10 mU/L and below 20 mU/L WB should be considered to have a borderline result and a repeat sample requested (7-10 days after the initial sample regardless of gestational age at birth). This should be reported as: CHT borderline (see chapter 6)

5.2 Insufficient sample: no re-assay possible

If it is not possible to punch any further discs from the card (i.e. for a single result ≥8 mU/L WB) then a repeat specimen, to be taken as soon as possible, should be requested due to insufficient sample.

5.3 Only one re-assay possible

If only two TSH results can be obtained (i.e. after initial analysis only one further spot from the card is possible) proceed as follows:

a) If the average of the two results is below the action cut-off (10 mU/L WB) report CHT not suspected unless the baby was born less than 32 weeks gestation – in this case, a repeat request should be issued (status code 03 “repeat sample required for CHT preterm” - see CHT Preterm Repeat Policy in chapter 7)
b) If the average of both results is $\geq 10$ mU/L, then proceed as per screening protocol (see Figure 2).

c) Widely discrepant results may require a repeat specimen, taken as soon as possible, to be requested – laboratory staff should use judgement on this.
6.0 The second specimen (i.e. repeat TSH test)

Requests for second blood samples for TSH testing will be made via locally agreed pathways defined as part of the newborn screening responsibilities.

6.1 Reason for repeat sample(s)

A second dried blood spot specimen for TSH screening is requested in the following situations:

- ‘CHT borderline’ has been reported

On detecting a borderline result, a second sample is to be taken 7-10 days after the initial sample.

The explanation to be given to parents is that a second sample is required to confirm the result (either positive or negative).

- A preterm baby (born at <32 weeks gestation) has had ‘CHT not suspected’ screening result on the first sample

The explanation to be given to parents is that in babies born at less than 32 weeks of pregnancy, the routine day 5 test may not pick up congenital hypothyroidism. It is advised to have another test at either 28 days of age or immediately before the baby is discharged home, whichever comes first.

The repeat request should be confirmed in writing to the appropriate health professional(s) outlining the reason for the repeat and when it should be completed.

6.2 Action on repeat sample(s)

The second dried blood spot specimen is for TSH testing only – it is recommended practice that other screening tests will not be repeated on this specimen.

The following are undertaken on the second sample depending on the reason for its request:

‘CHT borderline’ has been reported

- This second sample is assayed for TSH in duplicate, ideally from two different spots

- Babies with an average TSH concentration ≥10 mU/L whole blood (WB) in this second sample should be considered to have a positive screening result for CHT. This should be referred and reported as CHT suspected (see chapter 8).

- Babies with an average TSH concentration <10 mU/L WB in this second sample should be considered to have a negative screening result for CHT. This should be reported as CHT not suspected unless the baby was born less than 32 weeks gestation – in this case, a request should be issued (status code 03) for a repeat sample required for CHT preterm (see CHT Preterm Repeat Policy in chapter 7). The subsequent repeat sample should be treated the same as in the scenario below.

A preterm baby (born at <32 weeks gestation) with a previous (unreported) screening result of ‘CHT not suspected’
• This second sample is assayed for TSH in singleton and processed as per an initial screening sample

• Babies with an average TSH concentration ≥20 mU/L WB, in this second sample should be considered to have a positive screening result for CHT. This should be referred and reported as CHT suspected (see chapter 8)

• Babies with an average TSH concentration <10 mU/L WB in this second sample should be considered to have a negative screening result for CHT. This should be reported as CHT not suspected

• Babies with an average TSH concentration ≥10 mU/L WB and <20 mU/L WB in this second sample should be considered to have a borderline screening result for CHT. This should be reported as CHT borderline

On detecting a borderline result, a further sample is to be taken 7-10 days after the initial sample

The explanation to be given to parents is that a further sample is required to confirm the result (either positive or negative)

The following are undertaken on this subsequent sample:

• This subsequent sample is assayed for TSH in duplicate, ideally from two different spots

• Babies with an average TSH concentration ≥10 mU/L WB in this second sample should be considered to have a positive screening result for CHT. This should be referred and reported as CHT suspected (see chapter 8)

• Babies with an average TSH concentration <10 mU/L WB in this sample should be considered to have a negative screening result for CHT. This should be reported as CHT not suspected
### 7.0 Preterm Repeat Policy

#### 7.1 Policy

An expert sub-group comprising representatives from the British Society of Paediatric Endocrinology (BSPED), British Association of Perinatal Medicine (BAPM) and the UK Newborn Screening Laboratory Network (UKNSLN), reviewed the evidence and concluded that the optimal gestational age threshold for repeat testing is \( \geq 32 \) weeks gestation.

This decision was informed by published evidence including that from a study to clarify postnatal trends in postpartum serum thyroid hormones in preterm infants. Physiological evidence suggests that 28 days is the postnatal age by which maturation of thyroid function has occurred in most very preterm infants (Williams et al., 2004).

The policy involves the retesting of approximately 1.4% of babies who are born under 32 weeks gestation (Moser et al., 2007).

All babies born at 32 weeks gestation or under are admitted to a neonatal unit.

The policy is based on gestational age criteria and includes babies born at less than 32 weeks gestation (less than or equal to 31+6 days) and repeat testing at 28 days postnatal age, counting day of birth as day 0, or discharge home, whichever is the sooner (see Figure 3).

This policy for CHT screening in preterm infants was implemented in all four UK countries on 1st April 2012.

The written policy can also be found in the revised Guidelines for Newborn Blood Spot Sampling (UK Newborn Screening Programme Centre, 2012b) available at: [www.newbornbloodspot.screening.nhs.uk/bloodspotsampling](http://www.newbornbloodspot.screening.nhs.uk/bloodspotsampling).

The advantages of this policy are:

- Offer of screening is completed whilst the baby is an inpatient
- Access to the baby and responsibility for taking the sample is clear
- Better use of resources due to reduced need to chase for a repeat sample in the community
- Facilitates audit requirements

If babies are moved to another hospital, responsibility for taking the CHT preterm repeat sample (if less than 32 weeks) is transferred to the receiving hospital.
Gestational age must be recorded on the blood spot card for laboratory to report a valid CHT result.
8.0 Clinical follow-up and referral

8.1 Responsibility for communications / clinical liaison

Each screening laboratory should have an agreed arrangement for the follow-up and referral of all presumptive positive cases (i.e. CHT suspected - see section 2.1). This should be part of a comprehensive newborn screening service specification agreed with commissioners and local clinical services together with other newborn screening programmes. Responsibility for undertaking the referral must be documented and must include arrangements for back-up.

These arrangements should be regularly updated to reflect personnel changes and the evolution of clinical services. For further details see the CHT Initial Clinical Referral Standards and Guidelines (See Appendix 1 - UK Newborn Screening Programme Centre, 2013) available at: www.newbornbloodspot.screening.nhs.uk/cht.


8.2 Follow-up of CHT suspected cases

These are babies in any of the following situations where the average TSH concentration is:

- ≥20 mU/L whole blood (WB) on the initial screening sample or on a second sample for a preterm baby (<32 weeks gestation) or

- ≥10 mU/L WB in the second or subsequent sample following an initial borderline result

CHT suspected cases should be referred to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients. This should be completed according to locally agreed and documented procedures on the same or next working day of the definitive screening result becoming available. Appropriate failsafe mechanisms must be in place to ensure CHT suspected babies have entered into the diagnostic pathway (see Appendix 1 – Initial Clinical Referral Standards and Guidelines).

Clinicians should work to a common protocol and have access to the full range of diagnostic investigations where required.

The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby’s positive screening result.

A baby in whom a diagnosis of CHT has been made should commence treatment with oral levothyroxine by:

- a) CHT suspected on initial screening sample
  Acceptable standard: 17 days of age (100% of infants)
  Achievable standard: 14 days of age (100% of infants)

- b) CHT suspected on a repeat blood spot sample that follows a borderline TSH
  Acceptable standard: 24 days of age (100% of infants)
  Achievable standard: 21 days of age (100% of infants)
For further details see the CHT Initial Clinical Referral Standards and Guidelines (See Appendix 1 - UK Newborn Screening Programme Centre, 2013) available at: www.newbornbloodspot.screening.nhs.uk/cht.

8.3 Communication of CHT suspected

Laboratories shall notify a positive screening test (blood spot results expressed as a whole number), verbally and in writing by secure fax or email, to the lead paediatrician or deputy and the health professional responsible for communicating results. This notification should include a link to the standardised diagnostic and initial treatment protocol. This initiates the clinical referral of screen positive cases (see Appendix 3).

The result should be communicated to the family by an informed health professional. The health professional making initial contact should provide the following information to the family:

a) The NHS Newborn Blood Spot Screening Programme parent information leaflet ‘Congenital hypothyroidism is suspected’ (via hard copy or web link: www.newbornbloodspot.screening.nhs.uk/cht)

b) Details of the time and date of the appointment with the paediatrician and appropriate contact telephone numbers

Detailed guidelines have been developed by the NHS Newborn Blood Spot Screening Programme to support healthcare professionals in the communication of screening results to parents when CHT is suspected. See ‘Communication Guidelines: When Congenital Hypothyroidism is Suspected’ (UK Newborn Screening Programme Centre, 2012c) available at: www.newbornbloodspot.screening.nhs.uk/cht.

The outcome of the first appointment should be reported to the newborn screening laboratory.

The regional endocrine centre should also be informed about diagnostic outcome to facilitate regional and national audit.

See Appendix 1 for the full CHT Initial Clinical Referral Standards and Guidelines including the standardised diagnostic and initial treatment protocol.
9.0 Reporting and communication of results

Screening laboratories shall use the newborn screening results status codes for acknowledging the receipt of specimens in the laboratory and when reporting results to the child health records departments (CHRDs) - see status codes section 9.1.

‘CHT not suspected’ results should normally be communicated to the parents via health visitors. However, ‘CHT not suspected’ screening results following a second or further sample, should be communicated as soon as possible because anxieties will have been raised.

Results requiring follow-up/clinical referral of the baby (CHT suspected) are communicated directly to the parents by an appropriate health professional – see Appendix 3 – Communication Guidelines: When Congenital Hypothyroidism is Suspected.

For babies who are referred, the screening laboratory reports the results directly to the clinician to whom the child is referred. An example template suitable for written communication from the laboratory is available in Appendix 4 and also available on the NHS Newborn Blood Spot Screening Programme website (www.newbornbloodspot.screening.nhs.uk/cht).

Reports of all screening results should have a generic disclaimer attached: ‘These tests are screening tests; no screening test is 100% reliable’. Such a disclaimer is particularly relevant to CHT because of the variable nature of the condition (see section 3.3).

9.1 Status codes

The outcome from all newborn screening tests is described in the form of a status code for each blood spot card that is received for the baby. The status codes are used to report results to child health records departments, particularly when reporting electronically. Status codes for each blood sample must be maintained within the child health system clearly linked to the baby's record and the date of sampling. A baby may have blood taken for CHT screening as a first sample, a repeat for the first sample, a second sample taken because of prematurity and a repeat second sample if the initial ‘second’ sample is inadequate.

The status codes can be found on the NHS Newborn Blood Spot Screening Programme website and are summarised below for CHT (www.newbornbloodspot.screening.nhs.uk/statuscodes).
## Table 1. Status codes for CHT

<table>
<thead>
<tr>
<th>Code</th>
<th>Suggested term to be displayed in the child health system</th>
<th>Comments with reference to CHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Specimen received in laboratory</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>CHT screening declined</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>CHT – repeat/further sample required</td>
<td>Reasons for repeat sample will include the following pick list:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baby too young for reliable screening (&lt;5 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Too soon after transfusion (&lt;72 hours)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unsuitable sample (e.g. sample more than 14 days in transit, card out of date, Contamination)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insufficient sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unsatisfactory analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Preterm (&lt;32 weeks gestation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Borderline result</td>
</tr>
<tr>
<td>04</td>
<td>CHT not suspected</td>
<td><strong>First sample:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean [TSH] &lt; 8 mU/L whole blood (WB) (singleton assay) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean [TSH] &lt;10 mU/L WB (triplicate analysis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Second sample:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean [TSH] &lt;10 mU/L WB (duplicate analysis)</td>
</tr>
<tr>
<td>05</td>
<td>Not applicable to CHT</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Not applicable to CF</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>Not applicable to CF</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>CHT suspected</td>
<td><strong>These will include the following categories:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥20 mU/L whole blood (WB) on the initial screening sample or on a second sample for a preterm baby (&lt;32 weeks gestation) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥10 mU/L WB in the second or subsequent sample following an initial borderline result</td>
</tr>
<tr>
<td>09</td>
<td>CHT not screened/screening incomplete</td>
<td>Use with additional qualifying terms for: -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baby who has died i.e. before first sample/repeat sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unreliable result</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baby has been transferred out of screening laboratory area and is still awaiting the collection of a repeat first or second TSH sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not contactable, reasonable efforts made</td>
</tr>
<tr>
<td>10</td>
<td>Not applicable to CHT</td>
<td></td>
</tr>
</tbody>
</table>
10.0 Laboratory standards and guidelines

10.1 Generic standards
The NHS Newborn Blood Spot Screening Programme has generic standards for blood spot screening relating to completeness of coverage, timely identification of babies with a null or incomplete result, use of the NHS number as a unique identifier, timely sample collection and receipt, quality of the blood spot sample, timely taking of a repeat, laboratory accreditation, processing of screen positives, timely receipt into clinical care and timeliness of results to parents; these standards include CF screening.


10.2 Screening laboratory
Organisation

• Newborn blood spot screening shall be provided within the organisational structure of the newborn blood spot screening programme and undertaken by specialist newborn screening laboratories already providing screening programmes

• Laboratories undertaking newborn blood spot screening shall be accredited by Clinical Pathology Accreditation (UK) Ltd (CPA) now formally part of the United Kingdom Accreditation Service (UKAS). This shall include the newborn blood spot screening specialist assessment. There must be a senior member of laboratory staff at medical consultant or consultant clinical scientist level responsible for newborn blood spot screening with defined lines of accountability for all laboratory aspects of the service

• There shall be written agreed procedures describing the working arrangements between the screening laboratory and their referral laboratory

• There shall be documented local policies and standard operating procedures describing the whole screening process including pre-analytical, analytical and post-analytical processes. These shall include reporting of normal and abnormal results, referral and follow-up arrangements for presumptive positive cases. Processes shall be provided in line with relevant national standards and guidance and screening specifications. Processes shall be reviewed periodically taking into account audit data, accumulating results, technical developments and local changes in healthcare provision

• The laboratory must release reports on screening performance, including external quality assurance and CPA assessments to any agency with a legitimate interest in the quality and safety of the programme on behalf of the public
Analytical processes

• Assay for thyroid stimulating hormone (TSH) must be performed by an approved method capable of performing to the required sensitivity/specificity. Any proposal to introduce new analytical methods needs careful collective consideration by the Congenital Hypothyroidism Scientific Advisory Group and the Joint Standing Committee on Screening for Congenital Hypothyroidism and meet the recommended specification.

• Samples for diagnostic purposes should be sent to an accredited laboratory.

• Laboratories shall participate in audit at local, regional and national levels, to assess the effectiveness of the national screening programme.

• Laboratories should publish the results and performance of their newborn blood spot screening programme within an annual report.

• There shall be a documented risk management policy for the laboratory aspects of the CHT Screening Programme. These should describe the steps in the testing protocol where failures could occur and the procedures that have been implemented to minimise the risk of their occurrence.

• Screening incidents shall be managed in accordance with the UK National Screening Committee’s Managing Incidents in National NHS Screening Programmes – Interim Guidance (Sep 2013) (UK National Screening Committee, 2013).

10.3 Overall performance

Timeliness

• TSH analysis is timed to permit referral of screen positive results within 2-4 working days of sample receipt.

• The laboratory shall refer babies with positive screening results for CHT the same or next working day.

• Where referral is outwith a regional endocrine centre, the regional specialist team should be available to provide support and to facilitate access to diagnostic investigations where required.

• The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby’s positive screening result.

Quality assurance

• Laboratories undertaking newborn blood spot screening shall undertake internal quality control procedures for the screening test and demonstrate satisfactory performance in an approved external quality assurance scheme.
11.0 Data collection and audit

It is essential that data be collected to monitor the performance of the national CHT screening protocol, thus allowing us to assure parents that the screening works effectively in detecting clinically relevant CHT cases in infancy and also enable us to compare the national programme with that of other newborn screening programmes throughout the world.

The laboratory based data required (www.newbornbloodspot.screening.nhs.uk/datacollection) should be collected by the laboratory in each area and submitted on a retrospective basis to the NHS Newborn Blood Spot Screening Programme by the 31 July for the previous financial year (01 April - 31 March).

Clinical information (www.newbornbloodspot.screening.nhs.uk/datacollection) should be requested from clinical referral centres on each presumptive positive case. Data on each case notified should be collated and anonymised before submission to the NHS Newborn Blood Spot Screening Programme. Cases presenting clinically should also be anonymised and reported to the NHS Newborn Blood Spot Screening Programme.

It is the responsibility of the designated clinician to ensure that these forms are completed and returned to their respective laboratory directors.

If a screening laboratory director or clinical team is made aware of a CHT case that has not been detected via the CHT Screening Programme, it is very important that information on the case be reported to the NHS Newborn Blood Spot Screening Programme. The details should be gathered by the clinical team in conjunction with the laboratory director using the ‘Notification of CHT diagnosis for babies/children (up to the age of 5 years) not identified through the newborn screening programme’ form (www.newbornbloodspot.screening.nhs.uk/datacollection).

The screening laboratory should issue the relevant clinical team with this form (see section 2.3.1). The data should be collated and anonymised by the screening laboratory director and returned as soon as possible to NHS Newborn Blood Spot Screening Programme. Data on these cases will be collated on an annual basis as an important part of the audit of the programme.


We would like to thank Professor Anne Green, Dr. David Isherwood and Professor Rodney Pollitt for their major contribution to this document in the previous editions; Dr. Sarah Ball, Ms. Cathy Coppinger and Dr. Paul Newland for their contributions to this edition and to many contributors from the UK screening laboratories who provided valuable information.

Any comments on the content of this handbook should be sent for the attention of the CF Scientific Advisory Group c/o the NHS Newborn Blood Spot Screening Programme: phe.screeninghelpdesk@nhs.net.

### Appendix 1 CHT Initial Clinical Referral Standards and Guidelines (January 2013)

<table>
<thead>
<tr>
<th>Stage of process</th>
<th>No.</th>
<th>Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>The screening protocol</td>
<td>1</td>
<td>The initial screening sample – thyroid stimulating hormone (TSH) analysis is performed on a single spot from the initial dried blood sample. Samples with TSH ≥ a preliminary threshold (analytical cut off*) of 8 mU/L whole blood (WB) are re-tested in duplicate from the same card but on a different spot(s). Action is taken on the triplicate mean result. Second sample – TSH is analysed in duplicate and action taken on the duplicate result. (See screening protocol flow diagram p8). Timeliness of analysis – analysis is timed to permit referral of screen positive results within 2-4 working days of sample receipt. *The analytical cut off is set at 20% below the screen action cut off of 10 mU/L WB to allow for the natural variation in the TSH assay (i.e. the coefficient of variation, CV=10%) and to minimise the effect of volumetric variability that occurs in dried blood spots. Re-testing also acts as confirmation of correct sample identification.</td>
</tr>
<tr>
<td>Categorisation of initial screening result</td>
<td>2</td>
<td>Babies in whom the TSH concentration is &lt;10 mU/L WB on the initial screening sample should be considered to have a negative screening result for congenital hypothyroidism (CHT). Report CHT not suspected.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Babies in whom the TSH concentration is ≥20 mU/L WB on the initial screening sample should be considered to have a positive screening result for CHT. Report and refer as CHT suspected.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Babies in whom the TSH concentration is ≥10 and &lt;20 mU/L WB on the initial screening sample should be considered to have a borderline result for CHT.</td>
</tr>
<tr>
<td>Stage of process</td>
<td>No.</td>
<td>Standards</td>
</tr>
<tr>
<td>------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Borderline screening result</td>
<td>5</td>
<td>On detecting a borderline result, a second sample is to be taken 7-10 days after the initial sample.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>If the TSH concentration is &lt;10 mIU/L, WB on this second sample, the baby should be considered to have a negative screening result for CHT.</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Report CHT not suspected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If the TSH concentration is ≥10 mIU/L, WB on this second sample:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Report and refer as CHT suspected.</td>
</tr>
<tr>
<td>Referral of babies with positive screening results</td>
<td>8</td>
<td>The laboratory shall refer babies with positive screening results for CHT the same or next working day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referral is to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appropriate failsafe mechanisms must be in place to ensure CHT suspected babies have entered into the diagnostic pathway.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinicians should work to a common protocol and have access to the full range of diagnostic investigations recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Where referral is out-with a regional endocrine centre, the regional specialist team should be available to provide support and to facilitate access to diagnostic investigations where required.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby’s positive screening result.</td>
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<tr>
<td>Stage of process</td>
<td>No.</td>
<td>Standards</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-----</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Communication flows</td>
<td>10</td>
<td>Laboratories shall notify a positive screening test (blood spot results expressed as a whole number), verbally and in writing by secure fax or email, to the lead paediatrician or deputy and the health professional responsible for communicating results. This notification should include a link to the standardised diagnostic and initial treatment protocol. This initiates the clinical referral of screen positive cases.</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>The result should be communicated by an informed health professional. The health professional making initial contact should provide the following information to the family:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) The UK Newborn Screening Programme Centre parent information leaflet ‘Congenital hypothyroidism is suspected’ (via hard copy or web link)</td>
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<tr>
<td></td>
<td></td>
<td>b) Details of the time and date of the appointment with the paediatrician and appropriate contact telephone numbers</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>The outcome of the first appointment should be reported to the newborn screening laboratory.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The regional endocrine centre should also be informed about diagnostic outcome to facilitate regional and national audit.</td>
</tr>
<tr>
<td>Clinical evaluation and confirmatory diagnostic tests</td>
<td>13</td>
<td>The clinician responsible for assessing the baby with a positive screening result shall take a clinical history and perform a clinical exam.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(See note 1)</td>
</tr>
</tbody>
</table>

**Note 1:** Babies with CHT are more likely to have associated anomalies, particularly congenital heart defects and hearing loss and require careful neonatal examination and follow up. A complete history, including maternal thyroid status (previous history of thyroid dysfunction, maternal anti-thyroid medications), maternal diet (e.g. vegan or other low iodine diet) and family history should be obtained.
<table>
<thead>
<tr>
<th>Stage of process</th>
<th>No.</th>
<th>Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>Diagnostic tests considered essential in the baby are:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) Free T4 (plasma or serum)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) TSH (plasma or serum)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(See note 2)</td>
</tr>
<tr>
<td>Note 2: Diagnosis using free T4 and TSH should be performed on a plasma or serum sample using the appropriate age-related reference range as defined by the laboratory in relation to the equipment used.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desirable additional diagnostic tests</td>
<td>15</td>
<td>Appropriate imaging techniques (radioisotope and/or ultrasound scans) may help to establish whether the thyroid gland is:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) Normally situated and normal in size and shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Normally situated but abnormal in size and shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c) Ectopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d) Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(See note 3)</td>
</tr>
<tr>
<td>Note 3: A radioisotope scan and an ultrasound examination may establish the cause of the child’s CHT and indicate whether the condition is likely to be permanent. Initiation of treatment should not be delayed whilst waiting for an isotope scan, which can be performed up to 5 days after starting therapy. An ultrasound scan can be performed at any stage and investigation need not be confined to the neonatal period. These investigations may increase awareness of potentially related problems such as deafness and can provide information about recurrence risk. Recurrence is unusual in the case of thyroid dysgenesis but there is likely to be autosomal recessive inheritance with a 1:4 recurrence risk for families of babies with thyroid dyshormonogenesis. Both isotope scanning and thyroid ultrasound in neonates require specialist skills and can generate misleading results.</td>
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<tr>
<td>Stage of process</td>
<td>No.</td>
<td>Standards</td>
</tr>
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<td></td>
<td>16</td>
<td>In addition, the following test may be helpful:</td>
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<tr>
<td></td>
<td></td>
<td>a) Thyroglobulin</td>
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<td>(See note 4)</td>
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<td></td>
<td></td>
<td>Note 4: Plasma thyroglobulin needs to be measured on a sample taken prior to the start of treatment; this must not delay initiation of treatment. If plasma thyroglobulin is detectable then there must be some thyroid tissue present. Concentrations will be undetectable in thyroid agenesis.</td>
</tr>
<tr>
<td>Advisable tests in the mother</td>
<td>17</td>
<td>Diagnostic tests considered advisable in the mother to exclude interference in the infant’s TSH measurement and to exclude thyroid dysfunction in the mother include:</td>
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<tr>
<td></td>
<td></td>
<td>a) Free T4 (plasma or serum)</td>
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<td></td>
<td>b) TSH (plasma or serum)</td>
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<td></td>
<td>These investigations should be extended to include an assessment of TSH antibody receptor status in mothers with a current or previous history of autoimmune thyroid disease.</td>
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<tr>
<td>Treatment</td>
<td>18</td>
<td>A baby in whom a diagnosis of CHT has been made should commence treatment with oral levothyroxine by:</td>
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<tr>
<td></td>
<td></td>
<td>a) CHT suspected on initial screening sample</td>
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<td></td>
<td></td>
<td>Acceptable standard: 17 days of age (100% of infants)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Achievable standard: 14 days of age (100% of infants)</td>
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<tr>
<td></td>
<td></td>
<td>b) CHT suspected on a repeat blood spot sample that follows a borderline TSH</td>
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<tr>
<td></td>
<td></td>
<td>Acceptable standard: 24 days of age (100% of infants)</td>
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<tr>
<td></td>
<td></td>
<td>Achievable standard: 21 days of age (100% of infants)</td>
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<tr>
<td>Stage of process</td>
<td>No.</td>
<td>Standards</td>
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<td>19</td>
<td>The starting dose of oral levothyroxine should be 10-15 mcg/kg/day, with a maximum dose of 50 mcg/day. The objective of treatment is to normalise TSH within the first month. The dose of levothyroxine may need to be reduced if TSH is suppressed or if the baby is showing signs of overtreatment. Babies with significant endogenous thyroid hormone production may need smaller initial doses.</td>
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<td>(See note 5)</td>
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<td>20</td>
<td>Note 5: Treatment with levothyroxine should lead to normalisation of free T4 and a 50% reduction in TSH within days. However, TSH normalisation can take weeks and timing does not correlate well with the administered levothyroxine dosage or the severity of the underlying diagnosis. The aim of treatment is therefore to increase free T4 close to the upper reference range within the first 2 weeks of treatment and to normalise the TSH within the first month. Free T4 concentrations may exceed the normal reference range at the time of TSH normalisation but significant elevation should be avoided. Regular dose adjustments may be required.</td>
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<td>21</td>
<td>Only licensed solutions and tablets of levothyroxine should be used. Suspensions may be unreliable. Parents should be shown how to administer preparations and accompanying written information should be provided.</td>
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<td></td>
<td>22</td>
<td>Once levothyroxine treatment has been started, TSH and thyroid hormone concentration should be checked at an appointment with a paediatrician at approximately 2 weeks, 4 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after treatment is started, and thereafter as indicated. More intensive biochemical monitoring may be required. (See note 5)</td>
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<td></td>
<td>Assessment of permanence of hypothyroidism.</td>
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<td>In cases where the cause or persistence/permanence of hypothyroidism has not been confirmed (see diagnostic protocol flow diagram p9), confirmatory testing should be undertaken by stopping thyroxine at 2-3 years of age with thyroid function tests checked 4-6 weeks later. The outcome should be fed back to the regional endocrine centre to facilitate regional and national audit.</td>
</tr>
</tbody>
</table>
Diagnostic Protocol Flow Diagram

1. TSH elevated beyond the first 6/12 of life, either on T4 treatment or CHT confirmed by genetic testing

2. Hypothyroidism (agenesis, hypoplasia, or arrest of development)

3. Recomence thyroxine

4. TSH elevated after 4-6 weeks off T4 treatment

5. Possible transient CHT

6. TSH normal after 4-6 weeks off T4 treatment

7. Permanent CHT

8. Transient CHT
Appendix 2 British Paediatric Surveillance Unit (BPSU) study – UK Surveillance of Primary Congenital Hypothyroidism in Children Aged 5 Years and Under (UK CHT)

Beginning in June 2011, this UK study aims to determine how many babies and children up to and including five years of age are found each year to have primary congenital hypothyroidism (CHT), diagnosed subsequent to a presumed positive newborn screening test or because of clinical manifestations.

The researchers will describe their characteristics, diagnostic tests and initial treatment. Additional information will be collected about each child’s health after one and two years, particularly to define transient cases.

In a population covered by newborn screening, this study will enable researchers to determine the incidence and characteristics of children diagnosed with primary congenital hypothyroidism, the proportion and outcomes of those detected by screening, as well as to describe variations in clinical management and care.


For more information visit: www.rcpch.ac.uk/what-we-do/bpsu/current-studies/congenital-hypothyroidism/congenital-hypothyroidism.
Appendix 3 Communication Guidelines: When Congenital Hypothyroidism is Suspected

Communication Guidelines: When Congenital Hypothyroidism is Suspected

The following guidelines have been developed by the UK Newborn Screening Programme Centre (UKNSPC) to support healthcare professionals in their communication of screening results to parents when Congenital Hypothyroidism (CHT) is suspected.

<table>
<thead>
<tr>
<th>Guidelines for communicating screening results that indicate CHT is suspected</th>
<th>Reasoning</th>
</tr>
</thead>
</table>
| Parents should be told their baby’s result as soon as possible. | If the diagnosis is confirmed, the baby should be started on daily levothyroxine treatment as soon as possible.  
Parental anxiety will be raised if the CHT suspected outcome result was preceded by a TSH borderline result. |
| The result should be communicated by a well-informed health professional and ideally face-to-face.  
The setting must be appropriate e.g. if in person, in a quiet room; if by phone, check that the parent is free to listen.  
If they are alone, ask them if they would like you to contact someone to support them. | Parents prefer to be informed by someone with a good understanding of CHT and its management.  
A face-to-face explanation is best as the parents can ask questions. A telephone conversation may be appropriate if a face-to-face meeting is impractical or will cause delay. |
| The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby’s positive screening result. | The baby must be investigated by a paediatric endocrine team (regional specialist team) or by a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients as soon as possible.  
Parents should not be left without a clear management plan over a weekend or bank holiday after being informed of their baby’s positive screening result. |
<table>
<thead>
<tr>
<th>Guidelines for communicating screening results that indicate CHT is suspected</th>
<th>Reasoning</th>
</tr>
</thead>
</table>
| Standardised information should be provided to parents, for example:  
  - The screening result suggests that their baby may be affected by CHT  
  - Babies with CHT do not make enough of the hormone thyroxine, which is produced in a gland in the neck called the thyroid  
  - Their baby will need further tests to confirm this result  
  - That this treatment will improve their baby’s future health and enable him or her to grow and develop normally  
  - In most cases CHT happens by chance and the specific cause is not known. There is nothing the parents could have done to prevent it  
  - The time and place of their appointment and the name and contact details of the member(s) of the healthcare team  
  - That if a diagnosis of CHT is confirmed, their baby will need to be started on daily levothyroxine treatment very soon  
  - Parents should be provided with a copy of the results leaflet ‘Congenital hypothyroidism is suspected’. This can be downloaded from: [www.newbornbloodspot.screening.nhs.uk/cht suspected](http://www.newbornbloodspot.screening.nhs.uk/cht suspected)  
  - The health professional should give the family a contact number that they can call prior to their appointment with any questions or concerns | Parents can quickly forget or misunderstand verbal information about their baby’s results. Hence they should also be provided with reliable sources of information and support (as shown on the back of the ‘Congenital hypothyroidism is suspected’ leaflet). |
| Parents should be informed about all newborn blood spot screening test results and all results should be recorded in the Personal Child Health Record. | To ensure that the results of all five conditions for which babies are screened for, are communicated to parents. When one of the newborn screening conditions is suspected, parents do not receive a ‘normal results letter’ from the child health records department. |
| It is recommended that, where possible, health visitors are actively involved alongside specialists in the early stages of communicating results to parents, providing this does not delay communicating the result and starting treatment. | Health visitors have an on going role in supporting families. |
Appendix 4 Template for notification of presumptive positive for designated paediatrician (by screening laboratory to clinician)

For patient’s notes

Baby’s name ____________________________________________________________
Gender ________________________________________________________________
D.O.B _____________________________________________________________________
Birth weight ___________________________ Gestation ____________________________
NHS number __________________________________________________________________
Address _____________________________________________________________________

To the Paediatrician

The above baby was found to have a suspected (abnormal) newborn screening test for congenital hypothyroidism (CHT). The results for mean blood spot thyroid stimulating hormone (TSH) concentration were ___________________ mU/L whole blood. The screening tests for phenylketonuria, medium-chain acyl-CoA dehydrogenase deficiency (MCADD), sickle cell disease and cystic fibrosis are ________________________________________________________.

Recommended action as per CHT Screening Programme Initial Clinical Referral and Diagnostic Protocol (available from www.newbornbloodspot.screening.nhs.uk/cht):

• The first clinical appointment must take place on the same day or the next day after parents are informed of their baby’s screening result
• Complete clinical and family history including maternal thyroid status (previous history of thyroid dysfunction, maternal anti-thyroid medications), maternal diet (e.g. vegan or other low iodine diet) and clinical examination
• Essential diagnostic tests:
  o Free T4 (plasma or serum)
  o TSH (plasma or serum)
• Desirable additional diagnostic tests:
  o Appropriate imaging techniques (radioisotope and/or ultrasound scans)
  o Thyroglobulin (taken prior to starting treatment)
• Advisable tests in the mother:
  o Free T4 (plasma or serum)
  o TSH (plasma or serum)
  o Assess thyroid antibody receptor status if there is a current or previous history of autoimmune thyroid disease

Signed: ________________________________ Date: _________________________

Screening laboratory contact details: ________________________________________

Resources available from www.newbornbloodspot.screening.nhs.uk/cht:
‘Congenital hypothyroidism and your child’ leaflet
‘Communication Guidelines: When Congenital Hypothyroidism is Suspected’